

EXHIBIT A196

Special Report: Policy

A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres

In March, 2009, 27 scientists from eight countries met at the International Agency for Research on Cancer (IARC) to reassess the carcinogenicity of metals, arsenic, dusts, and fibres previously classified as “carcinogenic to humans” (Group 1) and to identify additional tumour sites and mechanisms of carcinogenesis (table). These assessments will be published as part C of Volume 100 of the IARC Monographs.

Inhalation is the primary route of exposure to arsenic in the workplace and happens in industries such as non-ferrous smelting, arsenic production, wood preservation, glass manufacturing, production and application of arsenic-based pesticides, and electronics. Non-occupational exposure to arsenic is mainly through food, except in areas with high levels of arsenic in the drinking water—eg, Taiwan, Bangladesh, West Bengal (India), northern Chile, and Cordoba Province (Argentina).¹ Epidemiological studies have shown that exposure to arsenic through inhalation or drinking-water

causes cancer of the lung, skin, and urinary bladder. Evidence suggests an association between exposure to arsenic in drinking water and the development of tumours at several other sites; however, various factors prevent a conclusion. Analytical studies have provided only limited information to support an association with kidney cancer, causes of liver cancer can be difficult to elucidate in groups that are high-risk for hepatitis B, and data on prostate cancer and arsenic exposure are not consistent between countries. Overall, the Working Group classified arsenic and inorganic arsenic compounds as “carcinogenic to humans” (Group 1). The organic arsenicals monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) are the active ingredients of some herbicides and are metabolites of inorganic arsenic. On the basis of sufficient evidence of cancer caused by DMA in experimental animals, and because MMA is extensively metabolised to DMA, both compounds are classified as “possibly carcinogenic

to humans” (Group 2B). Arsenobetaine and other organic arsenic compounds that are not metabolised in humans are “not classifiable” (Group 3).

The Working Group reaffirmed the classification of beryllium and its compounds, cadmium and its compounds, chromium (VI) compounds, and nickel compounds as “carcinogenic to humans” (Group 1). Studies involved complex occupational exposures to a metal and its compounds, making it impossible to separately assess their carcinogenicity.

Globally, an estimated 125 million people are still exposed to asbestos in the workplace.² Although asbestos has been banned or restricted in most of the industrialised world, its use is increasing in parts of Asia, South America, and the former Soviet Union.³ Naturally occurring sources of asbestos, its use in brake linings, and deterioration of asbestos-containing products all contribute to environmental exposure worldwide. Exposure may also come from fibres carried home on the clothing of asbestos workers.⁴



Upcoming meetings

June 2–9, 2009
Radiation
September 29–October 6, 2009
Lifestyle Factors
October 20–27, 2009
Chemical Agents and Related Occupations
<http://monographs.iarc.fr/>

Group 1 agent	Tumour sites (or types) for which there is sufficient evidence in humans	Other sites with limited evidence in humans	Established mechanistic events
Arsenic and inorganic arsenic compounds	Lung, skin, urinary bladder	Kidney, liver, prostate	Oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects, DNA-repair inhibition leading to mutagenesis
Beryllium and beryllium compounds	Lung	..	Chromosome aberrations, aneuploidy, DNA damage
Cadmium and cadmium compounds	Lung	Prostate, kidney	DNA-repair inhibition, disturbance of tumour-suppressor proteins leading to genomic instability
Chromium (VI) compounds	Lung	Nasal cavity and paranasal sinuses	Direct DNA damage after intracellular reduction to Cr(III), mutation, genomic instability, aneuploidy, cell transformation
Nickel compounds	Lung, nasal cavity, and paranasal sinuses	..	DNA damage, chromosome aberrations, genomic instability, micronuclei, DNA-repair inhibition, alteration of DNA methylation, histone modification
Asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite)	Lung, mesothelioma, larynx, ovary	Colorectum, pharynx, stomach	Impaired fibre clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signalling pathways, resistance to apoptosis
Erionite	Mesothelioma	..	Genotoxicity
Silica dust, crystalline in the form of quartz or cristobalite	Lung	..	Impaired particle clearance leading to macrophage activation and persistent inflammation
Leather dust	Nasal cavity and paranasal sinuses
Wood dust	Nasal cavity and paranasal sinuses, nasopharynx

Table: Metals, arsenic, dusts, and fibres assessed by the IARC Monograph Working Group

Monograph Working Group Members

U Heinrich—Co-Chair (Germany);
J Samet—Co-Chair (USA);
P A Demers, M Gérin,
J Siemiatycki (Canada);
P Grandjean (Denmark); A Aitio,
T Kauppinen (Finland);
M Goldberg (France); A Hartwig,
H Muhle (Germany); B Fubini,
F Merletti (Italy); M Ikeda
(Japan); M D Attfield, K P Cantor,
B A Fowler, R Henderson,
P F Infante, AB Kane,
P J Landrigan, R Lunn,
T G Rossman, L Stayner,
M P Waalkes, E M Ward, J M Ward
(USA)

Conflicts of interest

RH served as chair of the US EPA
Clean Air Seminar Advisory
Committee from 2004 to 2008,
which reviews US air standards
for noxious gases and particulate
matter. ABK is a member of the
Science Advisory Board for the
US EPA and served as chair of
their Working Group on Asbestos
in 2008.

Invited Specialists
None

Epidemiological evidence has increasingly shown an association of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) with an increased risk of lung cancer and mesothelioma. Although the potency differences with respect to lung cancer or mesothelioma for fibres of various types and dimensions are debated, the fundamental conclusion is that all forms of asbestos are “carcinogenic to humans” (Group 1). Mineral substances (eg, talc or vermiculite) that contain asbestos should also be regarded as “carcinogenic to humans”.

Sufficient evidence is now available to show that asbestos also causes cancer of the larynx and of the ovary. A meta-analysis of cohort studies reported a relative risk of cancer of the larynx of 1.4 (95% CI 1.2–1.6) for “any” exposure to asbestos. With different exposure metrics, the relative risk for “high” exposure versus “none” was at least 2.0 (1.6–2.5).⁵ Cohort studies of women who were heavily exposed to asbestos in the workplace consistently report increased risks of ovarian cancer, as in a study of women in the UK who manufactured gas masks during World War II.⁶ Studies suggest that asbestos can accumulate in the ovaries of women who are exposed to it.⁷

The Working Group classified the evidence for an association between asbestos and colorectal cancer as “limited”, although members were evenly divided as to whether the evidence was strong enough to warrant classification as “sufficient”. Further, there is “limited” evidence in humans for cancers of the pharynx and of the stomach.

The mechanism of the carcinogenicity of asbestos fibres involves a complex interaction between the crystalline mineral fibres and target cells. The physicochemical properties of asbestos fibres that are most relevant to pathogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Direct and indirect mechanisms have been

proposed on the basis of in-vitro cellular assays and acute and subchronic animal bioassays (table). Respiratory responses to inhalation of asbestos fibres are substantially different between species, and the biological mechanisms responsible for these differences are unknown.

The Working Group reaffirmed the carcinogenicity of crystalline silica dust as Group 1. An increased risk of lung cancer was observed across various industries and processes.⁸

The Working Group reviewed evidence of epidemiological studies of boot and shoe manufacture and repair, and found that sinonasal cancers can result from exposure to leather dust and leukaemias from exposure to benzene. A particularly high risk of sinonasal adenocarcinoma was noted among workers with the highest exposure to leather dust.⁹ Leather dust was classified as “carcinogenic to humans” (Group 1).

Epidemiological studies report a strong association between exposure to wood dust and development of sinonasal cancer.¹⁰ Only a few studies included details of tumour histology and substantial risks for sinonasal adenocarcinoma were noted. The few studies that assessed exposure to specific wood types found strong evidence of carcinogenicity for hardwood dusts. Case-control studies that investigated exposure to softwood dust observed a consistent but smaller risk, compared with hardwood dust, mainly for squamous-cell carcinoma. For cancer of the nasopharynx, exposure to formaldehyde is unlikely to be responsible for the increased risks (compared with the reference population) that were reported in most case-control studies and in the pooled reanalysis of cohort studies.¹¹ Wood dust was reaffirmed as “carcinogenic to humans”.

Kurt Straif, Lamia Benbrahim-Tallaa,
Robert Baan, Yann Grosse,
Béatrice Secretan, Fatiha El Ghissassi,
Véronique Bouvard, Neela Guha,
Crystal Freeman, Laurent Galichet,
Vincent Coglian, on behalf of the WHO

International Agency for Research on Cancer Monograph Working Group.
International Agency for Research on Cancer, Lyon, France

The IARC authors declared no conflicts of interest.

Attending the meeting as Representatives of their respective health agencies were P B Larsen (Danish Environmental Protection Agency), A Huici-Montagud (European Commission Directorate General for Employment, Social Affairs and Equal Opportunities), T Bateson and R Sams (US Environmental Protection Agency), and F Rice and M Schubauer-Berigan (US National Institute for Occupational Safety and Health). Attending the meeting as Observers sponsored by various organisations were J Addison (RT Vanderbilt Co, USA), D Bernstein and J Hoskins (American Forest and Paper Association), M G Bird (ExxonMobil Corp, USA), F Bochmann (German Social Accident Insurance), G Bromfield (Canadian Cancer Society), P Crosignani (International Society of Doctors for the Environment, Switzerland), D Deubner (Brush Wellman Inc, USA), M Eldan (Methanearsonic Acid Research Task Force, USA), J Gamble (National Stone, Sand and Gravel Association, USA), J Goodman (Eurometaux, Belgium), TK Grimsrud (Cancer Registry of Norway), E Kovalevskiy (Russian Academy of Medical Sciences), R A Lemen (private consultant, USA), P Morfeld and G Oberdörster (EUROSIL, Belgium; EUROTALC, Belgium; Industrial Minerals Association, North America, USA), L Neumeister (International Social Security Association, Germany), and A Oller (Nickel Producers Environmental Research Association Inc, USA).

- 1 IARC. Some drinking-water disinfectants and contaminants, including arsenic. *IARC Monogr Eval Carcinog Risks Hum* 2004; **84**: 1–477.
- 2 WHO. Elimination of asbestos-related diseases. http://whqlibdoc.who.int/hq/2006/WHO_SDE_OEH_06_03_eng.pdf (accessed April 9, 2009).
- 3 LaDou J. The asbestos cancer epidemic. *Environ Health Perspect* 2004; **112**: 285–90.
- 4 Anderson HA, Lillis R, Daum SM, Selikoff IJ. Asbestosis among household contacts of asbestos factory workers. *Ann NY Acad Sci* 1979; **330**: 387–99.
- 5 Institute of Medicine, Committee on Asbestos. Selected health effects. Asbestos: selected cancers. Washington, DC: National Academies Press, 2006.
- 6 Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med* 1982; **39**: 344–48.
- 7 Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. *Am J Ind Med* 1996; **29**: 435–39.
- 8 Steenland K, Mannetje A, Boffetta P, et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes Control* 2001; **12**: 773–84.
- 9 ‘tMannetje A., Kogevinas M, Luce D, et al. Sinonasal cancer, occupation, and tobacco smoking in European women and men. *Am J Ind Med* 1999; **36**: 101–07.
- 10 Demers PA, Boffetta P, Kogevinas M, et al. Pooled reanalysis of cancer mortality among five cohorts of workers in wood-related industries. *Scand J Work Environ Health* 21: 1995; 179–90.